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The sorption of nitroglycerin by infusion sets

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The sorption of nitroglycerin, from 5% glucose solution, by infusion sets was investigated under simulated perfusion conditions. Several burettes, sets and catheters were evaluated. The stability of the drug in the presence of glucose was also determined. High density polyethylene and glass proved satisfactory for its perfusion in solutions. A method for the evaluation of its uptake under simulated perfusion conditions is described.

Although extended literature is available on the sorption of nitroglycerin by materials used for infusion (Boylan et al 1978; Cossum et al 1978; Ludwig & Veda 1978; McNiff et al 1979; Baaske et al 1980; Christiansen et al 1980; Mathot et al 1980; Roberts et al 1980; Scheife et al 1982; Remon & Bogaert 1983), some controversy remains. For example, there is no consensus concerning the adsorption of the drug to glass and the effect of the composition of the infusion solution on the adsorption phenomenon (Bouyer et al 1984). This is mainly due to the different analytical techniques used. There is agreement in the literature about the losses of nitroglycerin kept in PVC containers (Remon & Bogaert 1983; Bouyer et al 1984), but little research has been done using an infusion system simulating hospital practice (Baaske et al 1980; Christiansen et al 1980). This we set out to do.

Materials and methods

Materials. In all experiments, an ethanolic 1% nitroglycerin solution was used (Merck, Darmstadt, W. Germany). Three burettes and five infusion sets were examined. The main specifications of the materials are given in Table 1.

Analysis and simulated infusions. The HPLC method described by Olsen & Scroggins (1983) was modified. The system consisted of a solvent pump (Waters Associates M 6000), a septumless syringe loaded injector loop of 10 μL (type CV-6-UHPa-N60, Valco Instr. Corp., Houston, USA) a 5 μm particle Rosil C18 HL column (25 cm × 4·6 mm, Alltech, Eke, Belgium) and a variable wavelength UV-detector (Pye Unicam LC3) set at 215 nm. The mobile phase was methanol–water (80 : 20 v/v). The flow rate was 1·0 mL min^{-1}.

Calibration curves (peak area versus concn) for a nitroglycerin concentration between 25 and 300 mg L^{-1}, dissolved in 5% glucose solution showed excellent correlation (Y = 0·694 X − 1·47; r = 0·9979). The standard deviation, calculated on the slope of the calibration curve, is 4·3% (n = 6).

Burettes and LVP-containers were sampled with a 0·5 mL glass syringe. During simulated infusion, one end of the infusion set or catheter was connected directly to the injector loop, allowing instant sampling. Because of the continuous flow through the loop, sampling was reproducible and the use of an internal standard with the risk of competitive sorption was omitted.

The column performance was monitored during the infusion experiment every 30 min, without stopping the infusion, by injecting a standard solution of 250 mg L^{-1} of nitroglycerin. Before the test, the stability of nitroglycerin was investigated in 5% glucose as well as in 0·9% NaCl solution using glass bottles (Table 1: code A) and PVC bags (code B) at 6, 20 and 40 °C in the dark and in daylight. The containers were stored upright, eliminating the influence of stoppers or silicon rubber parts.

Several burettes were tested for sorption by filling them with 100 mL of a 5% glucose solution containing 250 mg L^{-1} of nitroglycerin. Infusion sets without burettes were connected to glass bottles (code A) and the fluid flow of delivery of all sets was controlled by an Ivac infusion pump (type 131, Ivac Corporation, San Diego, USA), set at a droplet rate corresponding,

Table 1. Specifications of containers, infusion sets and catheters examined for nitroglycerin adsorption.

Code	Device	Material	Manufacturer
A	250 mL container	Glass	Baxter, Travenol Lessen, Belgium
B	250 mL bag	PVC	Baxter, Travenol Lessen, Belgium (Viaflex)
C	Burette	Cellulose propionate	Travenol, Lessen, Belgium (Buretrol)
D	Burette	Polystyrol-butadiene	Braun, Melsungen, W-Germ. (Dosifix)
E	Burette	HDPE	Miramed, Mirandola, Italy (Metriflo)
F	Giving-set and burette	PVC HDPE	Miramed, Mirandola, Italy (Metriflo)
G	Giving-set and burette	PVC Polystyrol-butadiene	Braun, Melsungen, W-Germ. (Dosifix)
H	Giving-set	PVC	Braun, Melsungen, W-Germany (Intrafix Ai)
I	Giving-set	PVC	Braun, Melsungen, W-Germany (Infusiomat)
J	Giving-set	PVC	Travenol, Lessen, Belgium (Travenol C2082)
K	Catheter	Polyurethane	Braun, Melsungen, W-Germ. (Cavafix Certo 325)
L	Catheter	Silicon rubber	Vygon SA, Ecouen, France (Vygon nr 278)
M	Catheter	Polyurethane	British Viggo, Swindon, UK (Secalon Seldy)

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respectively, to 3 and 15 mL h^{-1}. (These rates are based on realistic infusion data.) Attempts were made to presaturate the sets by initial rinsing with the glucose/nitroglycerin intravenous solution for 10 min at a flow rate of 3 mL min^{-1}.

Losses of nitroglycerin to catheters were investigated by using equal sized items (20 cm) connected to a glass container which supplied the glucose/nitroglycerin solution by gravity at a flow rate of 12 mL h^{-1}.

Results and discussion

The influence of temperature and daylight on the degradation and loss of nitroglycerin from LVP solutions in contact with glass (code A) and PVC (code B) is seen in Fig. 1A. As can be seen, the drug adsorbs onto glass containers filled with saline, an equilibrium being reached 6 h after contact indicating that there is no degradation. Its adsorption to glass was much lower when a glucose solution was used and the extent was temperature-dependent. The influence of daylight on the degradation of nitroglycerin in glass containers was minor and would seem to be negligible for hospital practice. On the contrary, a pronounced sorption of nitroglycerin was observed with solutions filled in PVC bags.

This result agrees with those of Bouyer et al (1984). Fig. 1B visualizes the sorption pattern of nitroglycerin by three PVC giving-sets. These curves can be described only by a multi-exponential equation because of the variability of the make-up of the different PVC sets. The results were quantified by calculating the area under the curve (concn of drug vs time) and were expressed as the percentage of the theoretical area for no drug loss (Table 2).

This method allowed the calculation of the amount of nitroglycerin delivered to the patient and the evaluation of its losses for a given infusion system and flow rate.

Table 2. Evaluation of the sorption of nitroglycerol (250 mg mL^{-1}) in 5% glucose infusion solution by different administration sets (n = 3).

	Flow rate mL h^{-1}	% Area under the curve g min L^{-1}
J	15	32·6 ± 3·2
		41·9 ± 2·1†
H	15	51·0 ± 2·9
		56·6 ± 2·0†
I	15	41·2 ± 4·0
		46·4 ± 3·6†
G*	15	47·6 ± 3·0
		53·0 ± 2·9†
F*	15	58·4 ± 3·5†
G*	3	29·0 ± 2·7
		39·8 ± 2·9†
F*	3	43·5 ± 3·1†

* With burette.
† Prerinsing 10 min/3 mL min^{-1}.

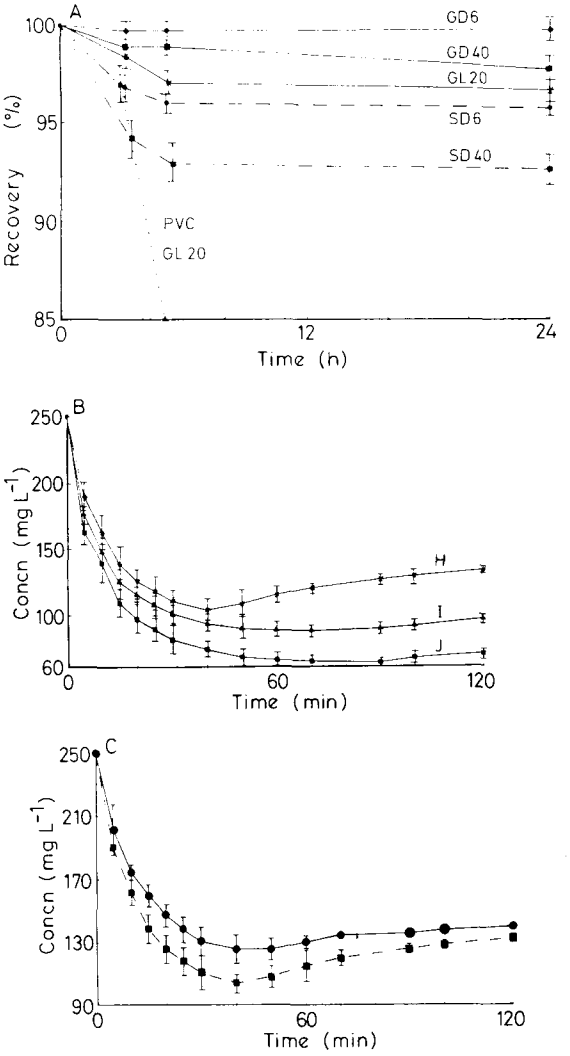

FIG. 1. A. Effect of the storage conditions on the stability of nitroglycerin infusion solutions in LVP containers (glass unless otherwise stated) stored upright. (Initial concentration 250 mg L^{-1}). G = 5% glucose. S = 0·9% NaCl. D = dark, L = light. Figures are °C. B. Concentration of nitroglycerin in 5% glucose solution after perfusion through PVC giving-sets (H, I and J; Table 1) (initial concentration 250 mg L^{-1}; flow rate 15 mL h^{-1}, set was not prerinsed). C. Influence of prerinsing of the giving-set on the loss of nitroglycerin in 5% glucose solution. Set = Code H, initial concentration: 250 mg L^{-1} (●) set prerinsed (30 mL at 3 mL min^{-1}), (■) set not prerinsed; bars = standard error of the mean, (n = 3).

Each experiment was performed threefold. Fig. 1C shows, as an example, the standard error of the mean for the loss of the drug to a PVC giving-set (code H), with and without prerinsing with the infusion solution. Although the influence of prerinsing on the recovery of drug is obvious, the saturation of the PVC polymer was not achieved. Sorption of the drug by the polymer

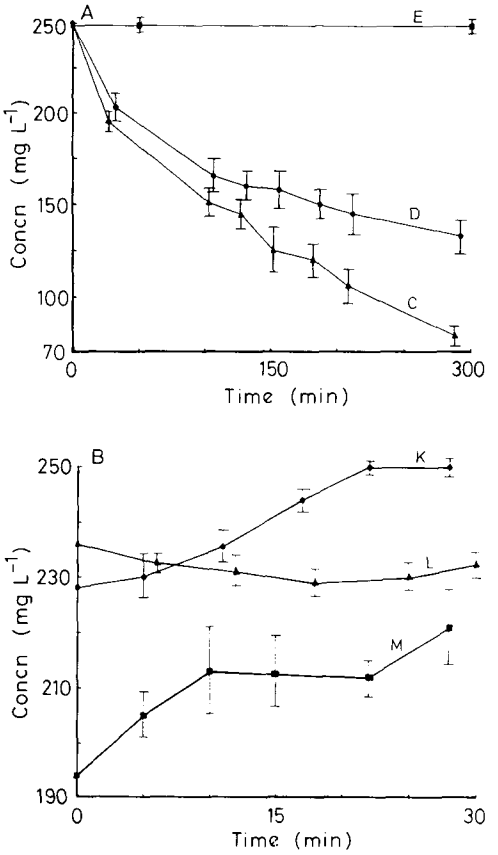

FIG. 2. A. Loss of nitroglycerin in 5% glucose solution to different burettes (C, D and E; Table 1) (initial concentration 250 mg L^{-1}). B. Loss of nitroglycerin in 5% glucose solution to different catheters (K, L and M; Table 1).

seemed to be time- and flow rate-dependent. It is obvious that concentrations of nitroglycerin in the effluent of the PVC giving-sets, will never reach the original concentration under normal infusion conditions.

All the sets investigated showed sorption of the drug which could result in an unpredictable pharmacological response during infusion.

Fig. 2A shows the results of the comparative study of the sorption of the drug from solution by several burettes. The high density polyethylene burette (code E), in contrast to cellulose propionate (code C) and polystyrolbutadiene (code D) burettes, exhibited no adsorption.

Only minor uptake was observed following the sorption of nitroglycerin by various catheters (Fig. 2B). Compared with the giving-sets, this sorption of the drug by the catheters may be considered of minor importance.

As can be seen from Fig. 2B at time zero an initial loss of nitroglycerin had already occurred. This could be explained by the method of nitroglycerin detection occurring at the end of the catheters. Time zero was considered as the moment of first passage of infusion fluid through the detector. At that moment part of the nitroglycerin has been sorbed.

The results as a whole indicate that the giving sets and the use of burettes are the major causes of the poor availability of nitroglycerin infusions, the best materials for handling nitroglycerin solutions being high density polyethylene and glass.

Conclusion. The effect of daylight on the stability of the drug was negligible so black tubing is not recommended. There is little sorption of the drug by catheters, but PVC giving sets and administration sets made of PVC also should be tested.

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